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Smoking as a risk factor for cystoid macular edema complicating intermediate uveitis

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Abstract

Purpose—To describe risk factors for the presence of cystoid macular edema (CME) among patients presenting with intermediate uveitis.

Design—Cross-sectional study.

Methods—*Setting:* Single-center, academic practice. *Study population:* 208 patients with intermediate uveitis evaluated from 1984 through September 2006. *Procedures:* Clinical and demographic data were entered retrospectively into a database and analyzed. *Outcome measures:* Presence of CME at presentation to our clinic; risk factors for presenting with CME.

Results—Of the 208 patients, 74% had bilateral intermediate uveitis, yielding 363 affected eyes. 89 patients (43%) had CME in at least one eye at the time of presentation to our clinic. After controlling for potentially confounding variables including demographics, duration of disease, active intraocular inflammation, history of diabetes mellitus or hypertension, and presence of epiretinal membrane, actively smoking at presentation was associated with a 4-fold increased risk of CME at presentation versus never smoking (OR = 3.90, 95% CI: 1.43, 10.66, P = 0.008). Former smoking also appeared to increase the risk CME at presentation in the multivariate analysis, but the result was of borderline statistical significance (OR = 1.97; 95% CI: 0.99, 3.94, P = 0.055). After adjusting for confounding, there was a 4% increased risk of CME at presentation for each cigarette smoked per day (OR = 1.04, 95%CI: 1.01, 10.7, P = 0.005).

Conclusions—Cystoid macular edema was a common structural ocular complication observed in our cohort. Current smoking was associated with a dose-dependent increased risk of having CME at the time of presentation to our clinic.

Introduction

Intermediate uveitis describes intraocular inflammation primarily located in the vitreous that may be associated with the presence of exudate along the pars plana (snowbanks) or

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condensation of inflammatory cells and debris in the vitreous (snowballs). The most common structural ocular complication observed in intermediate uveitis is cystoid macular edema (CME), which has been reported to occur in 20% to 44% of patients with intermediate uveitis, and is a major potential cause of visual loss among these patients.^{1–5} Because of the association with visual loss, identifying risk factors for the presence of CME among patients with intermediate uveitis could be helpful to the management of these patients. We therefore sought to identify risk factors for CME in a cross-sectional cohort of 208 consecutive patients with intermediate uveitis presenting to a single tertiary center, with a primary interest in smoking as a potential risk factor for presenting with CME.

Methods

Study population

All patients with intermediate uveitis who were seen by the Division of Ocular Immunology at the Wilmer Eye Institute between July 1984 and September 2006 were included in this study. Serologic testing for syphilis, Lyme antibody testing, and screening chest X-rays were performed on patients in order to detect other common causes of intermediate uveitis. Additional diagnostic tests including antibodies for toxoplasmosis, Toxocara, and Bartonella, were performed when clinically indicated. Only patients with non-infectious intermediate uveitis were included in this study. The study was performed with the approval of the Johns Hopkins University School of Medicine Institutional Review Board in accordance with the Declaration of Helsinki.

Data collection

Patients with intermediate uveitis were identified from a database that was established in 1984. Clinical information from the presenting examination of each patient evaluated for intermediate uveitis was collected by retrospective chart review. The data included demographic characteristics, past medical and ophthalmic histories, ophthalmologic examination at presentation, results of diagnostic testing, and medications that patients were taking at the time in which they presented to our clinic. Ophthalmologic examinations included measurement of best-corrected visual acuity using Snellen charts, intraocular pressure assessment, and findings from the slit lamp and dilated fundus examinations at presentation. Use of corticosteroids and of immunosuppressive drugs, either prior to or at the time of presentation also was collected. Data were entered on a computer-based, standardized data entry form for statistical analysis.

Main outcome measure

The frequency of CME observed at presentation was assessed. Cystoid macular edema was defined as the presence of macular thickening with cyst formation that was seen by clinical examination. Confirmation by fluorescein angiography or by optical coherence tomography was utilized when available.⁶

Statistical analysis

Frequencies of variables were tabulated for patients and for affected eyes. “By person” analyses were performed to evaluate potential risk factors for presence of CME in either eye at presentation. For these risk factor analyses, crude and adjusted odds ratios (OR) were calculated using univariate and multivariate logistic regression. For the multivariate logistic regression analyses, all statistically significant variables ($p < 0.05$) from the univariate analyses were included as well as variables that were thought to be potentially confounders. The variables included in the multivariate analyses were: age at presentation, race, duration of uveitis, history of diabetes mellitus and hypertension, presence of active intraocular inflammation, presence of epiretinal membrane, prior history of prednisone and immunosuppressive agents, and use

of topical corticosteroids, prednisone, and immunosuppressive drugs at presentation. Because we were interested in treatment effects, use of prednisone and immunosuppressive drug therapy prior to and at the time of presentation were “forced” into the multivariate analyses in order to look for potential associations. All analyses were performed using Intercooled Stata 9.0 statistical software (Stata Corporation, College Station, TX).

Results

Study Population

Characteristics at presentation of 208 patients with intermediate uveitis are summarized as Table 1. The median age at the diagnosis of intermediate uveitis was 30 years and the median age of patients at the time of presentation was 37 years (range: 6 to 76 years). The majority of patients were women (66%), Caucasian (91%), and had bilateral intermediate uveitis (74%). Thirty-six percent of patients had pars planitis based on Standardization of Uveitis Nomenclature (SUN) criteria (intermediate uveitis with snowbanking or snowballs and without an associated medical condition).⁶ Approximately 31% of patients had at least one systemic disease, including multiple sclerosis in 5%, sarcoidosis in 2%, hypertension in 8%, and diabetes mellitus in 3% of patients. Prior to presentation, 47% of patients had been treated with topical corticosteroids for their uveitis, 36% of patients had been treated with oral corticosteroids, 38% with periocular corticosteroid injections, 5% with intravenous corticosteroids, and 3% with immunosuppressive drugs at some point during their uveitis course. At presentation, 11% of patients were taking systemic corticosteroids and 3% were taking immunosuppressive drugs for intermediate uveitis. Eighty-nine of the 208 patients (43%) had CME at presentation in either eye, and 95 patients (46%) had either CME at presentation or a history of CME prior to presentation in either eye.

At presentation, 30% of patients were actively smoking and 14% of patients smoked previously but had quit. Of those patients who were smoking when they presented to our clinic, the median number of cigarettes smoked per day was 20 or one pack, and the median duration of smoking was 10 years.

Of the 363 eyes affected with intermediate uveitis, visual acuity of 20/50 or worse was present in 31% and 20/200 or worse acuity in 10%. Approximately 43% of eyes (156 eyes) had CME at presentation. Forty percent of eyes had active inflammation in the vitreous at the time of presentation.

Risk factors for CME in either eye at presentation

Demographic and clinical characteristics associated with the presence of CME in either eye at presentation are summarized as Table 2. In the univariate analyses, presence of active intraocular inflammation at presentation, use of systemic corticosteroids prior to presentation, and smoking at the time of presentation were statistically significant risk factors for the presence of CME in at least one eye with intermediate uveitis. After controlling for potentially confounding variables, patients who had been treated with systemic corticosteroids prior to presentation and patients who were currently smoking at presentation were more likely to have CME in at least one eye at the time in which they presented to our clinic (odds ratio [OR] = 4.28, 95% confidence interval [CI]: 1.97, 9.29, $P < 0.001$ and OR = 2.60, 95% CI: 1.33 5.09, $P = 0.005$, respectively). Analyses that evaluated potential risk factors for CME present in any affected eye (a “by eye”) yielded similar results (data not shown).

Effect of smoking on presence of CME in either eye at presentation

The association between cigarette smoking and presence of CME was evaluated further and the results are summarized as Table 3. In univariate and multivariate analyses, being a current

smoker at presentation was a statistically significant risk factor for having CME at presentation (OR = 2.09, 95% CI: 1.19, 3.65, $P = 0.01$) or having ever had CME either at or prior to presentation to our clinic (OR = 2.12, 95% CI: 1.21, 3.70, $P = 0.008$). When compared to patients who had never smoked, current smokers were at higher risk for having CME at presentation than were former smokers after adjusting for confounding (OR = 3.90, 95% CI: 1.43, 10.66, $P = 0.008$ and OR = 1.97, 95% CI: 0.99, 3.94, $P = 0.055$). Among current smokers, there appeared to be a dose response in that there was an increased risk of having CME at presentation among patients that smoked a greater number of cigarettes per day. For every additional cigarette smoked per day, the risk of presenting with CME was increased by an estimated 4%. The number of years smoked was not a statistically significant risk factor for having CME at presentation.

Discussion

We reviewed our experience with intermediate uveitis over 21 years. As in all retrospective studies, our results must be interpreted with caution. A referral bias may exist because our institution is a tertiary care medical center, and it is possible that only the more severe cases of intermediate uveitis were referred to our center. The observations that approximately 20% of patients had a history of CME prior to presentation and received therapy with oral corticosteroids prior to presentation could support this referral bias. Furthermore, a treatment by indication bias likely explains the association between prior systemic corticosteroid therapy and presence of CME at presentation, since patients with CME would be more likely to receive oral corticosteroids as therapy. However, the frequency of CME at presentation in our study was similar to the frequencies reported at other tertiary care centers.^{2–5} There also are limitations inherent to the use of cross-sectional data, such as the difficulty in assessing temporal associations or cohort effects. Our sample size may have limited the precision of the odds ratios for certain risk factors and increased the likelihood of a type II error, particularly for the multivariate analyses. Missing data also might have affected risk estimates, although smoking data at presentation was available for 96% of patients and for all other variables, data were complete in 98% or greater of patients. Furthermore, since the data on smoking were based on patient reporting, it is possible that these data are inaccurate as patients may have underestimated the average number of cigarettes they smoke per day (e.g., reporting bias). Despite these potential limitations, this study confirms that CME is observed frequently in intermediate uveitis seen in the tertiary care setting and suggests that smoking may be a significant risk factor for its occurrence.

Smoking has been implicated to have deleterious effects on many organs including the eye. Approximately 4000 active compounds have been identified in tobacco smoke and several are believed to be toxic to the eye, causing damage to ocular tissues via ischemic and/or oxidative mechanisms.⁷ Smoking has been reported to be a risk factor in the development of cataracts,^{8–10} age-related macular degeneration,^{11,12} thyroid-associated ophthalmopathy,¹³ anterior ischemic optic neuropathy,⁷ and primary open-angle glaucoma.^{14,15} There also has been a suggestion that smoking may delay the effect of therapy for certain ocular conditions such as scleritis¹⁶ and thyroid-associated ophthalmopathy.^{13,17}

The potential effects of smoking on the development and course of CME in intermediate uveitis have been described previously,¹ although the available published literature is limited. Helm and Holland reported a weak association between response to treatment and history of no smoking in their cohort of 20 patients with intermediate uveitis who were treated with posterior subtenon injections (PST) of triamcinolone acetonide. Five of the six patients (83%) without improvement in visual acuity after initial PST injection were smokers (versus 29% of patients with improved vision after first PST injection were smokers, $P = 0.07$). However, the study size was small and only 4 patients (20%) had CME at presentation.¹

The exact mechanism by which smoking might cause macular edema is not known. The deleterious effects of smoking on vascular endothelium have been well reported,¹⁸ and the retinal vasculature also is known to respond abnormally to hyperoxia in smokers.¹⁹ Endothelial dysfunction appears to be one of the earliest pathological effects of cigarette smoking,²⁰ and it is plausible that this damage leads to leakage of the retinal blood vessels resulting in macular edema. Because other systemic diseases (i.e., diabetes mellitus and hypertension), mechanical factors (i.e., vitreoretinal traction from epiretinal membrane formation), and active intraocular inflammation may predispose patients with intermediate uveitis to have CME through a similar mechanism, these variables were controlled for in the analyses. Age was also considered a potential confounding variable as patients under the age of 15 are less likely to have a history of smoking and older patients may have had a longer duration of uveitis and/or be more likely to have other diseases that might effect the retinal vasculature that we were unable to control for. However, after controlling for these potentially confounding variables, smoking remained a statistically significant risk factor for CME at the presenting examination.

We observed a borderline significant association between former smoking and the presence of CME at presentation ($P = 0.055$). We however did not have data on when patients quit smoking relative to their presentation to our clinic and therefore were unable to discern if the duration of no smoking modified the risk of CME. Longitudinal data would help to better determine if cessation of smoking is associated with a reduced risk of CME. Data on the effect of smoking cessation would be of interest, as it is a potentially modifiable risk factor, and the lower risk among former smokers, suggests that cessation may be of benefit.

In summary, almost one-half of our cohort of patients with intermediate uveitis had CME at the time in which they presented to our clinic. When compared to patients who had never smoked, actively smoking at the time of presentation was associated with an estimated 4-fold increased risk of CME after controlling for potentially confounding variables including patient age, disease duration, active intraocular inflammation, and presence of epiretinal membrane. This association appeared to be dose-dependent, although larger numbers of patients are required in order to discern a possible dose response among smokers with a 2-pack-per-day or higher usage. Further studies utilizing longitudinal data would be helpful to determine if smoking cessation decreases the risk of CME during follow up.

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D. Statement about Conformity: This study was approved by the Johns Hopkins University School of Medicine's IRB in accordance with the Declaration of Helsinki. This study is in compliance with HIPAA regulations.

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Table 1
Characteristics of Patients with Intermediate Uveitis at Presentation

Patient-specific characteristics	
Number of patients	208
Median age at diagnosis of IU, years (range)	30 (5–76)
Median age at presentation of IU, years (range)	37 (6–76)
Median duration of IU prior to presentation, years (range)	1.5 (0–3.5)
Gender, % women	66.4
Race, % Caucasian	91.4
Bilateral disease, %	74.5
Intermediate uveitis type	
% Primary intermediate uveitis	64.0
% Pars planitis subtype	36.0
Systemic diseases	
% Multiple Sclerosis	4.8
% Sarcoidosis	2.4
% Inflammatory bowel disease	1.9
% Cancer	2.9
% Hypertension	7.7
% Diabetes mellitus	3.4
% Other autoimmune	7.7
Therapies before presentation	
History of topical corticosteroids, %	46.6
History of oral corticosteroids, %	36.0
History of intravenous corticosteroids, %	4.8
History of periocular corticosteroid injections, %	38.5
History of carbonic anhydrase inhibitors, %	1.4
History of immunosuppressive drug therapy, %	3.4
Therapies at time of presentation	
Topical corticosteroids, %	25.5
Oral corticosteroids, %	10.6
Periocular corticosteroid injection, %	1.4
Immunosuppressive drug therapy, %	2.9
Smoking	
Never, %	51.0
Former, %	14.4
Current, %	30.3
Unknown, %	4.3
Median cigarettes per day, years (range)	20 (5–40)
Median duration of smoking, years (range)	10 (1–45)
Median pack-years (range)	13 (1–80)
Eye-specific characteristics	
Number of affected eyes with IU	363
Visual acuity	
20/50 or worse	31.3
20/200 or worse	10.0
Ocular Findings and Complications, %	
Ocular hypertension	8.0
Keratic precipitates	5.4
Posterior synechiae	4.1
Anterior chamber cell (> 0.5+ cells)	15.3
Vitreous cells (> 0.5+ cells)	40.3
Vitreous haze (> 1+ cells)	18.7
Snow balls	18.5
Snow banking	12.2
Epiretinal membrane	6.3
Cystoid macular edema	
CME at presentation	42.8
CME prior to presentation	18.3
CME ever	45.7
Cataract	9.1
Optic nerve disease	1.9
Retinal detachment	1.9
Band keratopathy	0.5

CME = cystoid macular edema; IU = intermediate uveitis

Table 2

Risk factors for having cystoid macular edema at presentation among patients with intermediate uveitis

Characteristic	Crude OR (95% CI) *	P-value	Adjusted OR* (95% CI) [†]	P-value
Age at presentation	1.01 (0.99, 1.03)	0.24		
Sex (male vs female)	0.91 (0.51, 1.63)	0.76		
Race (white vs nonwhite)	2.83 (0.90, 8.92)	0.08	3.78 (0.87, 14.65)	0.06
Duration of uveitis (years)	0.96 (0.90, 1.02)	0.15	0.93 (0.83, 1.02)	0.06
History of diabetes mellitus (yes vs no)	0.52 (0.10, 2.76)	0.48		
History of hypertension (yes vs no)	1.80 (0.64, 5.03)	0.26		
Active intraocular inflammation [†] (yes vs no)	1.91 (1.03, 3.56)	0.04	2.10 (0.84, 5.29)	0.10
Epiretinal membrane (yes vs no)	1.96 (0.75, 5.09)	0.17		
Prior systemic corticosteroids (yes vs no)	2.54 (1.42, 4.54)	0.002	4.28 (1.97, 9.29)	<0.001
Prior immunosuppressive drug therapy (yes vs no)	0.52 (0.10, 2.77)	0.45	0.16 (0.02, 2.35)	0.18
Topical corticosteroids at presentation (yes vs no)	0.84 (0.44, 1.58)	0.59		
Systemic corticosteroids at presentation (yes vs no)	1.13 (0.46, 2.74)	0.79		
Immunosuppressive drug therapy at presentation (yes vs no)	1.35 (0.26, 6.85)	0.72		
Current smoking (yes vs. no)	2.09 (1.19, 3.65)	0.01	2.60 (1.33, 5.09)	0.005

* Only those risk factors with P-values ≤ 0.10 shown.

[†] Defined as presence of either vitreous cell $\geq 0.5+$ or vitreous haze $\geq 1+$ or anterior chamber cell $\geq 0.5+$.

Table 3
Association between cystoid macular edema (CME) at presentation and smoking among patients with intermediate uveitis

Risk factor	OR	95% CI	P-value
Smoking status at presentation *			
Current	3.90	1.43 – 10.66	0.008
Former	1.97	0.99 – 3.94	0.055
Never (reference)	1.00		
Among current smokers at presentation *			
1 pack / day	2.36	1.25 – 4.43	0.008
½ pack/day	2.33	1.13 – 4.09	0.020
¼ pack/day	2.13	1.07 – 4.24	0.031
Cigarettes /day	1.04	1.01 – 1.07	0.005

CME = cystoid macular edema; OR = odds ratio; CI = confidence interval; P = P-value

* All analyses adjusted for age at presentation, duration of intermediate uveitis, gender, race, topical steroid therapy, oral steroid therapy, diabetes, hypertension, active intraocular inflammation, and presence of epiretinal membrane.